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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,046	08/09/2001	James McSwiggen	MBHB00-814-A (400/034US)	4737

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,046	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27,45,46,49,50 and 61-76* is/are pending in the application.

4a) Of the above claim(s) *62, 64-72, 74, and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27,45,46,49,50,61,63,73 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of SEQ ID NO: 143 and 2332 and the hammerhead species in the reply filed on 2/28/05 is acknowledged. The traversal is on the ground(s) that the ribozymes of the claimed method all target the same gene. Applicant asserts that since the target sequences are all subsets of the targeted gene, all the ribozymes should be examined together. Applicant also asserts that searching over 3000 distinct sequences would not be a burden but would be a simple undertaking that would only require 3 steps. This is not found persuasive because the sequences of the claimed method are distinct for the reasons provided in the restriction mailed 9/27/04. Applicant has not argued the specific reasons provided for requiring restriction between the specific sequences of the invention other than to assert that there is a core sequence which provides the function of CLCA1 nucleic acid cleavage. It is noted that the core sequence refered to would be present in any hammerhead ribozyme targeted to any known gene. The structure that provides the function of cleaving at any particular site relies upon the structure/sequence of the flanking arms which are not interchangeable to provide cleavage at different cites, for example. In response to applicant6s assertion for ease of nucleic acids searches the following is presented: MPEP 808.02 states in part:

Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05(C) - 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must shown by appropriate explanation one of the following:

(C) A different field of search: Where it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown, even though the two are classified together.

It is noted that a search of the available sequence databases produces a listing of references disclosing the sequence most similar to the query sequence. This is the "place" where the examiner searches for prior art. The prior art relating to another query sequence will not be found in this "place"- a different listing of references must be generated and searched by the examiner. Thus a different search is shown, and restriction is proper.

If applicant believes that the examiner is still in error in the assertion of a search burden and wishes to supply the office with a search strategy and completed relevancy ranked nucleic acid search, the examiner would take such information into consideration in so far as a rejoinder of the specific sequences.

The requirement is still deemed proper and is therefore made FINAL.

Claims (62, 64, 66, 68, 70, 72, 74, and 76) and (65, 67, 69, 71) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species respectively, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/28/05.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-27, 45, 46, 49, 50, 61, 63, 73, and 75 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to the treatment of a patient that has a condition associated with the level of CLCA1 via the administration of a nucleic acid that down regulates expression of CLCA1 under conditions suitable for treatment. The invention is so broad as to encompass the treatment of of any disease that is associated with CACL1 levels including but surely not limited to Chronic pulmonary Disease, chronic bronchitis, asthma, cystic fibrosis, obstructive bowel syndrome. The specification asserts that included would be "any other diseases [other than those cited above] that are related or will response to levels of CLCA1 in a cell or tissue, alone or in combination with other therapies (see page 10 of the specification as filed). The scope of nucleic acids for use in the method includes ribozymes antisense triplex etc where nucleic acids targeting CLCA1 are only required to have 50-75% complementarity to the target (Claims 61, 6373, and 75 are limited to hammerhead ribozymes targeting

CLCA1). The claimed invention is so broad as to read on the targeting of any CLCA1 gene (any allele, mutant etc. . .) from any species of animal.

The specification as filed provides a general teaching of antisense techniques but provides no specific guidance for the treatment of any particular disease. The specification provides a list of ribozyme structures based on cleavage sites on the nucleic acid recognized for cleavage by various ribozyme motifs. The specification as filed does not show the cleavage of any target with any of the thousands of ribozyme structures disclosed in the specification. The specification indicates that various CLCA1 genes from different species have various expression patterns (see pages 1and 2, for example). The specification asserts at Example 7 that emerging data in murine models of mucos hypersecretion in the tracea and lung indicate a correlation between mucous hypersecretion in the lung and strong upregulation of gob-5, a murine homologue of hCLCA1.

The specification does not show inhibition of CLCA1 in human cells or tissues. The specification does not provide examples that would show by correlation the treatment of any specific CLCA1 associated disease. The specification appears to provide a strating point for theclaimed method but fails to provide sufficient guidance such that undue experimentation would not be required to practice the invention.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than

was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from

most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is nt clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

The instant specification fails to provide any specific teaching for the delivery of any particular ribozyme to any particular animal to treat any particular disease associated with CACL1 levels such that one in the art would not be left to perform undue trial and error experimentation. The unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction regarding the direction in which the experimentation should proceed renders the invention not enabled.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635